## Title

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# Assessment of Potential Risk Levels Associated with U.S. Environmental Protection Agency Reference Values

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**The U.S. Environmental Protection Agency (U.S. EPA) generally uses reference doses (RfDs) or reference concentrations (RfCs) to assess risks from exposure to toxic substances for noncancer health end points. RfDs and RfCs are supposed to represent lifetime inhalation or ingestion exposure with minimal appreciable risk, but they do not include information about the estimated risk from exposures equal to the RfD/RfC. We used results from benchmark dose modeling approaches recently adopted for use in developing RfDs/RfCs to estimate the risk levels associated with exposures at the RfD/RfC. We searched the U.S. EPA Integrated Risk Information System (IRIS) database and identified 11 chemicals with oral RfDs and 12 chemicals with inhalation RfCs that used benchmark dose modeling. For assessments with sufficient model information, we found that 16 of 21 (76%) of the dose–response models were linear or supralinear. We estimated the risk from exposures at the established RfDs and RfCs for these chemicals using a linear dose–response curve to characterize risk below the observed data. Risk estimates ranged from 1 in 10,000 to 5 in 1,000 for exposures at the RfDs, and from 1 in 10,000 to 3 in 1,000 for exposures at the RfCs. Risk estimates for exposures at the RfD/RfC values derived from sublinear dose–response curves ranged from 3 in 1,000,000,000 to 8 in 10,000. Twenty-four percent of reference values corresponded to estimated risk levels greater than 1 in 1,000; 10 of 14 assessments had points of departure greater than the no-observed-adverse-effect levels. For policy development regarding management of cancer risks, the U.S. EPA often uses 1 in 1,000,000 as a *de minimis* risk level. Although noncancer outcomes may in some instances be reversible and considered less severe than cancer, our findings call into question the assumption that established RfD and RfC values represent negligibly small risk levels. *Key words:* benchmark dose, noncancer, risk assessment. *Environ Health Perspect* 111:1318–1325 (2003). doi:10.1289/ehp.6185 available via *http://dx.doi.org/* [Online 12 May 2003]**

Methods for evaluating risks from exposure to toxic substances for noncancer health end points (such as birth defects, respiratory effects, and hepatotoxicity) are based on the theory that there is a threshold below which there is negligible risk of adverse health effects from environmental exposures. At the U.S. Environmental Protection Agency (U.S. EPA), this negligible risk is quantified through the use of reference doses (RfDs) and reference concentrations (RfCs). The RfD or RfC is defined as an estimate of daily or continuous exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime (U.S. EPA 1999a). The value of the RfD or RfC is derived by determining a point of departure divided by uncertainty factors (UFs), which are used to account for uncertainties in the available studies, such as limitations in the database, variability within humans, and differences in species response (i.e., animal-to-human extrapolation).

The point of departure in environmental health risk assessment is meant to represent the lowest dose within the range of experimental data. In past practices, the point of departure was exclusively based on a no-observed-adverse-effect level (NOAEL) or a lowest-observed-adverse-affect level (LOAEL), derived from animal or epidemiologic studies. The NOAEL is the highest dose for which there are no observed statistically or biologically significant increases in the frequency or severity of adverse effects between the exposed population and its control. Similarly, the LOAEL is the lowest dose at which there are statistically or biologically significant increases in the frequency or severity of adverse effects between the exposed population and its appropriate control group. The NOAEL/LOAEL structure, however, does not provide sufficient information to quantify the equivalent risk levels from exposure at the RfD/RfC because there is no estimated risk at the NOAEL or LOAEL itself. Several authors have criticized the use of the NOAEL because of its sensitivity to sample size, the high sampling variability from experiment to experiment, and the inability to use all of the available dose–response data (Barnes et al. 1995; Crump 1984; Gaylor et al. 1998; Leisenring and Ryan 1992; U.S. EPA 2000a). Leisenring and Ryan (1992) have shown that average risk levels associated with the NOAEL may be substantial. The true risk of exposure at the NOAEL can vary from zero to > 20%, depending on the end point, spacing of doses, and numbers of animals used (Leisenring and Ryan 1992). In many cases, an adverse effect may not be detected in a critical effect study because of insufficient statistical power.

Although the NOAEL/LOAEL structure does not provide sufficient information to quantify risk levels from exposure (Gaylor and Kodell 2000), the resulting RfDs and RfCs are assumed to be equivalent to negligible or *de minimis* risks. As a point of comparison, the U.S. EPA has defined 1 in 1,000,000 excess cancer risk as a *de minimis* risk level for cancer (Caldwell et al. 1998; Clean Air Act Amendments 1990; Fiori and Meyerhoff 2002; U.S. EPA 1991), although regulatory actions are sometimes limited to instances where risk exceeds 1 in 100,000.

Over the past several years, the U.S. EPA has been in the process of developing the benchmark dose (BMD), which is derived from modeling the exposure–response data, as an alternative to the NOAEL/LOAEL as the point of departure for noncancer risk assessments. The BMD is the dose that corresponds to a specified level of increased response [the benchmark response (BMR)] compared with background. This dose is calculated by fitting a mathematical model to the dose–response data, which can be continuous or quantal. The BMD method has several advantages over the NOAEL/LOAEL method, including making better use of dose–response information and reflecting sample size more appropriately (Barnes et al. 1995; Crump 1995). In single-chemical hazard assessments, the BMD allows for consideration of the dose–response over the entire exposure range, and furthermore, when a dose derived from benchmark modeling is used as the point of departure, actual risk levels can be calculated as an alternative to the hazard index (which is typically based on comparisons of human exposures with an RfD or RfC).

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In 2000, the U.S. EPA published a draft guidance document on the application of the BMD approach in determining the point of departure for all types of health effects data (U.S. EPA 2000a). Although a BMR of 10% has most often been used by the U.S. EPA in its assessments, it is anticipated that 5% or 1% would be a more appropriate response level for some end points and designs. Furthermore, in these draft guidelines, a lower statistical confidence limit on the BMD (BMDL) is specifically proposed as a replacement for the NOAEL/LOAEL in setting the point of departure, which is used to determine acceptable levels of human exposure to environmental toxicants. A lower confidence limit is placed on the BMD to obtain a dose (BMDL) that assures with high confidence (e.g., 95%) that the BMR is not exceeded (U.S. EPA 2000a). In addition to ensuring an added measure of protection, this process rewards better experimental design and procedures that provide more precise estimates of the BMD.

Most new and revised RfDs and RfCs in the U.S. EPA Integrated Risk Information System (IRIS) assessments are based on BMD modeling. Certain health end points, however, are not amenable to modeling, and the NOAEL/LOAEL approach will continue to be used in some cases (U.S. EPA 2000a). For this article, we have reviewed and synthesized currently available risk assessment information on the chemicals for which U.S. EPA reference values are based on BMD modeling. We estimate the equivalent risk levels expected from hypothetical human exposures at established RfD and RfC values using the BMD dose–response information to investigate whether these levels represent negligible risks, and to underscore some of the potential strengths of using benchmark modeling in environmental health risk assessment.

## Methods

We searched the U.S. EPA IRIS database (U.S. EPA 2000b) to identify the chemicals for which current regulatory reference values relied on BMD modeling. We identified 11 chemicals with RfDs based on oral BMD values, and 12 chemicals with RfCs based on benchmark concentration (BMC) values. The BMD and

**Table 1.** Risk assessment information for chemicals with oral RfDs derived from benchmark modeling.[a]

| Chemical | NOAEL (mg/kg/day) | LOAEL (mg/kg/day) | $BMD_{10}$ (mg/kg/day) | $BMDL_{10}$ (mg/kg/day) | $BMD_{05}$ (mg/kg/day) | $BMDL_{05}$ (mg/kg/day) | BMD/BMDL | UF | RfD (mg/kg/day) |
|---|---|---|---|---|---|---|---|---|---|
| Quantal end point | | | | | | | | | |
| Beryllium and compounds (U.S. EPA 1998a) | 0.1 | — | 1.4 | 0.46[b] | — | — | 3.0 | 300 | 0.002 |
| Chloroform[c] (U.S. EPA 2001b) | — | 15 ($12.9_{ADJ}$) | 1.7 ($1.5_{ADJ}$) | 1.2 ($1.0_{ADJ}$)[b] | — | — | 1.4 | 100 | 0.01 |
| 1,1-Dichloroethylene (U.S. EPA 2002a) | 9 | 14 | 6.6 | 4.6[b] | — | — | 1.4 | 100 | 0.05 |
| 1,3-Dichloropropene (U.S. EPA 2000c) | 2.5 | — | 5.1 | 3.4[b] | — | — | 1.5 | 100 | 0.03 |
| Hexachlorocyclopentadiene (U.S. EPA 2001d) | — | 10 ($7_{ADJ}$) | 11 | 6[b] | — | — | 1.8 | 1,000 | 0.006 |
| Continuous end point | | | | | | | | | |
| Benzene[d] (U.S. EPA 2003) | — | 1.2 | 2.2 | 1.2[b] | — | — | 1.8 | 300 | 0.004 |
| EGBE[e] (U.S. EPA 1999b) | — | 59 | — | — | $7.7_{HED}$ | $5.1_{HED}$[b] | 1.5 | 10 | 0.5 |
| Methylmercury (U.S. EPA 2001a) | — | — | — | — | $1.4–2.6E^{-03}$ | $0.9–1.5E^{-03}$[b] | 1.6 | 10 | 0.0001 |
| Naphthalene[f] (U.S. EPA 1998i) | 100 ($71_{ADJ}$)[b] | 200 ($143_{ADJ}$) | 171($122_{ADJ}$) | 130 ($93_{ADJ}$) | — | — | 1.3 | 3,000 | 0.02 |
| Phenol[g] (U.S. EPA 2002c) | 60 | — | 157 | 93[b] | — | — | 1.7 | 300 | 0.3 |
| Tributyltin oxide (U.S. EPA 1997a) | 0.025 | — | 0.05 | 0.034[b] | — | — | 1.5 | 100 | 0.0003 |

Abbreviations: ADJ, adjusted for duration of exposure; $BMD_{10}$, BMD that equals a BMR of 10%; $BMDL_{10}$, lower confidence limit on the $BMD_{10}$; $BMD_{05}$, BMD that equals a BMR of 5%; $BMDL_{05}$, lower confidence limit on $BMD_{05}$; $C_{max}$, peak blood concentration; EGBE, ethylene glycol monobutyl ether; HED, human dose of an agent that is believed to induce the same magnitude of toxic effect as the experimental animal species concentration or dose (this adjustment may incorporate toxicokinetic information on the particular agent, if available, or use a default procedure, such as assuming that daily oral doses experienced for a lifetime are proportional to body weight raised to the 0.75 power).
[a]The reported number of significant figures is not standardized in IRIS. [b]Point of departure. [c]RfD derived from the LOAEL (1,000-fold UF) = 0.01 mg/kg/day; BMD-based RfD (100-fold UF) = 0.01 mg/kg/day. [d]Oral $BMDL_{[ADJ]}$ was derived from the $BMCL_{[ADJ]}$ (8.2 mg/m$^3$) by route-to-route extrapolation with the assumptions that inhalation absorption was 50% and oral absorption was 100% in the dose range near the BMC; BMDL (adjusted for continuous exposure) = (8.2 mg/m$^3$ × 20 m$^3$/day × 0.5)/70 kg = 1.2 mg/kg/day; former RfD derived from the LOAEL (1,000-fold UF) = 0.001. [e]HED was calculated as follows: using $C_{max}$ for 2-butoxyacetic acid as the dose metric, the $BMDL_{05}$ was determined to be 64 μM; physiologically based pharmacokinetic modeling was used to "back-calculate" a human equivalent dose of 5.1 mg/kg/day, assuming that rats and humans receive their entire dose of EGBE from drinking water over a 12-hr period each day. [f]RfDs were based on the NOAEL and $BMD_{10}$ values adjusted for duration (e.g., BMD × 5/7 days); the RfD in IRIS is derived from the NOAEL (3,000-fold UF) = 0.02 mg/kg/day; prospective RfD derived from BMD (3,000-fold UF) = 0.03 mg/kg/day. [g]BMD was based on a benchmark response of a 1-standard-deviation change from the control mean.

**Table 2.** End points and UFs for chemicals with oral RfDs derived from benchmark modeling.

| Chemical | Reference | End point: quantal or continuous | Composite UF | UF[a] | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | Interspecies | Intraspecies | Subchronic | Database | ELE |
| Beryllium and compounds | U.S. EPA 1998a | Quantal (small intestinal lesions) | 300 | 10 | 10 | — | 3 | — |
| Chloroform | U.S. EPA 2001b | Quantal (fatty cyst formation in liver and elevated serum glutamate-pyruvate transaminase) | 100 | 10 | 10 | — | — | — |
| 1,1-Dichloroethylene | U.S. EPA 2002a | Quantal [liver toxicity (fatty change)] | 100 | 10 | 10 | — | — | — |
| 1,3-Dichloropropene | U.S. EPA 2000c | Quantal (chronic irritation of stomach) | 100 | 10 | 10 | — | — | — |
| Hexachlorocyclopentadiene | U.S. EPA 2001d | Quantal (chronic irritation of stomach) | 1,000 | 10 | 10 | 3[b] | 3[b] | — |
| Benzene | U.S. EPA 2003 | Continuous (decreased lymphocyte count) | 300 | — | 10 | 3 | 3 | 3 |
| EGBE | U.S. EPA 1999b | Continuous (changes in mean corpuscular volume) | 10 | — | 10 | — | — | — |
| Methylmercury | U.S. EPA 2001a | Continuous (developmental neuropsychologic impairment) | 10 | — | 10 | — | — | — |
| Naphthalene | U.S. EPA 1998i | Continuous (decreased mean terminal body weight in males) | 3,000 | 10 | 10 | 10 | 3 | — |
| Phenol | U.S. EPA 2002c | Continuous (decreased maternal body weight gain) | 300 | 10 | 10 | — | 3 | — |
| Tributyltin oxide | U.S. EPA 1997a | Continuous (immunosuppression; decrease in IgE titer) | 100 | 10 | 10 | — | — | — |

Abbreviations: EGBE, ethylene glycol monobutyl ether; ELE, effect level extrapolation factor.
[a]Interspecies extrapolation, intraspecies differences (human variability), subchronic-to-chronic extrapolation, database deficiencies, and ELE. [b]UFs assigned a value of $10^{1/2}$ were rounded to 3.

BMC values and other risk assessment information for these chemicals are presented in Tables 1–4 (U.S. EPA 1995a, 1995b, 1995c, 1995d, 1997a, 1998a, 1998c, 1998e, 1998g, 1999b, 2000c, 2001a, 2001b, 2001d, 2002a, 2002c, 2002e, 2003). We have included risk assessment information for naphthalene, a chemical with an IRIS assessment containing an established RfD based on a NOAEL (RfD = 0.02 mg/kg/day) as well as a prospective RfD based on BMD modeling (RfD = 0.03 mg/kg/day) (U.S. EPA 1998i).

We determined whether the principal study identified for each chemical's IRIS assessment was derived from quantal (dichotomous) or continuous critical effect data (Tables 2 and 4). For compounds with BMD or BMC values based on quantal data, the BMR is expressed in terms of a percent increase in risk of adverse outcome compared with background. For compounds with BMD or BMC values based on continuous data, the BMR may be expressed as a percent change in mean response compared with control (e.g., immunosuppression with tributyltin oxide) or in terms of a 1 standard deviation change from the control mean response (e.g., decreased lymphocyte count with benzene). The BMR is a response level used to define a BMD, which is used as the point of departure, from which an RfD or RfC can be developed. The BMR is typically set at the lower end of the range of responses (e.g., 10% or 5% change) that can be detected experimentally. This can help to avoid uncertainties associated with low-dose extrapolation using models that may not reflect biologic realities (Crump 1995).

Using the benchmark modeling information described above from the IRIS assessments of 19 chemicals, we estimated the equivalent risk levels expected from hypothetical human exposures at the established RfDs and RfCs. We also evaluated whether each of the models used for BMD calculations was linear, sublinear, or supralinear in the observed dose range (Table 5) [National Research Council (NRC) 2000; U.S. EPA 1995a, 1995b, 1995c, 1995d, 1997b, 1998b, 1998c, 1998d, 1998f, 1998h,

**Table 3.** Risk assessment information for chemicals with RfCs derived from benchmark modeling.[a]

| Chemical | NOAEL | LOAEL | $BMC_{10}$ | $BMCL_{10}$ | $BMCL_{10[ADJ]}$ | $BMCL_{10[HEC]}$ | $BMC_{05}$ | $BMCL_{05}$ | BMC/BMCL | UF | RfC |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Quantal end point | | | | | | | | | | | |
| Antimony trioxide[b] (U.S. EPA 1995b) | 0.51 ($0.42_{HEC}$) | — | 1.43 | 0.87 | 0.16 | 0.074[c] | — | — | 1.6 | 300 | 0.0002 |
| 1,3-Butadiene (U.S. EPA 2002e) | — | 2.5 | 2.25 | 1.98[c] | — | — | — | — | 1.1 | 1,000 | 0.002 |
| 1,1-Dichloroethylene (U.S. EPA 2002a) | 99.2 ($17.7_{HEC}$) | 297.8 ($53.2_{HEC}$) | 59.95 | 38.9 | — | 6.9[c] | — | — | 1.5 | 30 | 0.2 |
| 1,3-Dichloropropene (U.S. EPA 2000c) | $3.7_{ADJ}$ | $14.9_{ADJ}$ | $5.91_{ADJ}$ | — | 3.66 | 0.72[c] | — | — | 1.6 | 30 | 0.02 |
| Methyl methacrylate (U.S. EPA 1998e) | 102.4 ($18.2_{ADJ}$) | — | 178.7 | 143 | 25.6 | 7.2[c] | — | 104.6 | 1.2 | 10 | 0.7 |
| Methylene diphenyl diisocyanate (U.S. EPA 1998g) | 0.2 ($0.036_{ADJ}$) | 1.0 ($0.18_{ADJ}$) | $0.22_{ADJ}$ | — | 0.14 | 0.06[c] | — | — | 1.6 | 100 | 0.0006 |
| Phosphoric acid (U.S. EPA 1995d) | 50 ($2.7_{ADJ}$) | 180 | 150 | 100 | 5.4 | 3.4[c] | 112 | 64 | 1.5 | 300 | 0.01 |
| 1,1,1,2-Tetrafluoroethane (U.S. EPA 1995a) | $7,450_{HEC}$ | $37,250_{HEC}$ | — | 46,000 | 8,200 | 8,200[c] | — | — | — | 100 | 80 |
| Continuous end point | | | | | | | | | | | |
| Benzene[d] (U.S. EPA 2003) | — | $8.7_{ADJ}$ | 43.77 | 23 | 8.2[c] | — | — | — | 1.9 | 300 | 0.03 |
| Carbon disulfide[e] (U.S. EPA 1995c) | 15.9 ($5.7_{ADJ}$) | 39.2 ($14.0_{ADJ}$) | — | 55.1 | 19.7[c] | — | — | — | — | 30 | 0.7 |
| Chromium VI (particulates) (U.S. EPA 1998c) | — | 0.05 | 0.036 | 0.016 | 0.034[c] | — | — | — | 2.3 | 300 | 0.0001 |
| EGBE (U.S. EPA 1999b) | — | $150_{HEC}$ | — | — | — | — | $530_{HEC}$ | $380_{HEC}$[c] | 1.4 | 30 | 13 |

Abbreviations: ADJ, dose that has been adjusted for duration of exposure; $BMC_{10}$, BMC that equals a BMR of 10%; $BMCL_{10}$, lower confidence limit on the $BMC_{10}$; $BMC_{05}$, BMC that equals a BMR of 5%; $BMCL_{05}$, lower confidence limit on $BMC_{05}$; HEC, human equivalent concentration [the human concentration (for inhalation exposure) of an agent that is believed to induce the same magnitude of toxic effect as the experimental animal species concentration or dose; this adjustment may incorporate toxicokinetic information on the particular agent, if available, or use a default procedure, such as assuming that daily oral doses experienced for a lifetime are proportional to body weight raised to the 0.75 power]; MVh, human ambient default minute volume; MVho, human occupational default minute volume; RDDR, regional deposited dose ratio (the ratio of the regional deposited dose calculated for a give exposure in the animal species of interest to the regional deposited dose of the same exposure in a human; this ratio is used to adjust the exposure effect level for interspecies dosimetric differences to derive a human equivalent concentration for particles).

[a]The reported number of significant figures is not standardized in IRIS. [b]Point of departure is the $BMCL_{10[HEC]}$ ($BMCL_{10[HEC]} = BMC_{10[ADJ]} \times RDDR = 0.074$ mg/m$^3$. [c]Point of departure. [d]BMC was based on a benchmark response of a 1-standard-deviation change from the control mean; the BMCL is the statistical lower bound estimate on the dose corresponding to a 1-standard-deviation change from control. [e]BMC is based on an 8-hr time-weighted average occupational exposure; its point of departure is $BMCL_{10[HEC]} = 55.1$ mg/m$^3$ × (MVho/MVh × 5/7 days) = 19.7 mg/m$^3$. MVho = 10 m$^3$/day; MVh = 20 m$^3$/day.

**Table 4.** End points and UFs for chemicals with RfCs derived from benchmark modeling.

| Chemical | Reference | End point: quantal or continuous | Composite UF | UF[a] | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | Interspecies | Intraspecies | Subchronic | Database | ELE |
| Antimony trioxide | U.S. EPA 1995b | Quantal (pulmonary toxicity, chronic interstitial inflammation) | 300 | 3 | 10 | 3 | 3 | — |
| 1,3-Butadiene | U.S. EPA 2002e | Quantal (ovarian atrophy) | 1,000 | 3 | 10 | — | 3 | 10 |
| 1,1-Dichloroethylene | U.S. EPA 2002a | Quantal [liver toxicity (fatty change)] | 30 | 3 | 10 | — | — | — |
| 1,3-Dichloropropene | U.S. EPA 2000c | Quantal (hyperplasia of nasal epithelium) | 30 | 3 | 10 | — | — | — |
| Methyl methacrylate | U.S. EPA 1998e | Quantal (degeneration/atrophy of olfactory epithelium) | 10 | 3 | 3 | — | — | — |
| Methylene diphenyl diisocyanate | U.S. EPA 1998g | Quantal (hyperplasia of the olfactory epithelium) | 100 | 3 | 10 | — | 3 | — |
| Phosphoric acid | U.S. EPA 1995d | Quantal (bronchiolar fibrosis) | 300 | 3 | 10 | 10 | — | — |
| 1,1,1,2-Tetrafluoroethane | U.S. EPA 1995a | Quantal (Leydig cell hyperplasia) | 100 | 3 | 10 | — | 3 | — |
| Benzene | U.S. EPA 2003 | Continuous (decreased lymphocyte count) | 300 | — | 10 | 3 | 3 | 3 |
| Carbon disulfide | U.S. EPA 1995c | Continuous (peripheral nervous system dysfunction) | 30 | — | 3 | — | 10 | — |
| Chromium VI (particulates) | U.S. EPA 1998c | Continuous (lactate dehydrogenase in bronchioalveolar lavage fluid) | 300 | 3 | 10 | 10 | — | — |
| EGBE | U.S. EPA 1999b | Continuous (changes in red blood cell count) | 30 | — | 10 | — | — | 3 |

Abbreviations: EGBE, ethylene glycol monobutyl ether; ELE, effect level extrapolation factor.

[a]Interspecies extrapolation, intraspecies differences (human variability), subchronic-to-chronic extrapolation, database deficiencies, and ELE.

1998j, 1999c, 2000d, 2001c, 2001e, 2002b, 2002d]). To estimate the risk level of the derived RfDs and RfCs, which have a linear or supralinear dose–response curve at the BMD/BMC, we assumed that the dose–response curves for these compounds are linear at doses below the BMD or BMC (Figure 1). For two assessments, sufficient information was not available to determine the shape of the dose–response curve (carbon disulfide and 1,1,1,2-tetrafluoroethane), and we assumed linearity [this assumption did not overly bias our results because linearity or supralinearity was the shape of the dose–response curve in approximately three-quarters (16 of 21) of cases in which the shape of the dose–response curve was discernable]. This assumption of linearity at the relevant part of the dose–response curve is necessary to extrapolate equivalent risk levels from U.S. EPA reference values derived from BMD modeling, and it is consistent with methods proposed in the U.S. EPA draft cancer risk assessment guidelines (U.S. EPA 1999d). Such risk-level extrapolation is not possible using the NOAEL/LOAEL approach.

Methods for risk-level estimation varied between reference values based on quantal end points and those based on continuous end points. For BMD/BMC values derived from quantal critical effect data, we estimated risk from exposure at concentrations equal to established RfD and RfC values by extrapolating linearly from the point represented by the BMR at the BMDL/BMCL to the established RfD and RfC values (Figure 1). We divided the risk at the BMR by the composite UF for those BMD models that were linear or supralinear. For example, to estimate risk from exposure to chloroform's RfC, we divided the estimated risk level at the point of departure (1 in 10 for BMR = 10%) by the composite UF of 100, to arrive at a risk of 1 in 1,000. For BMD/BMC values derived from continuous critical effect data (normally distributed), a change in response of 1 standard deviation from control is considered roughly equivalent to a 10% increase in risk of adverse response from exposure (e.g., benzene's BMR = change of 1 standard deviation in lymphocyte count compared with control mean) (U.S. EPA 2000a, 2003). Therefore, when data quality and distribution allowed, we treated the dose that resulted in a 1-standard-deviation change from control as equivalent to $BMD_{10}/BMC_{10}$ (BMD that equals a BMR of 10%/BMC that equals a BMR of 10%) values derived from quantal data. For assessments based on sublinear dose–response curves, we estimated risk of exposure at the RfD/RfC dose levels by extrapolating the BMD model response function to the RfD/RfC (i.e., using the BMD model, we estimated risk by putting the exposure equal to the RfD/RfC in the model).

For all chemicals in our assessment group with adequate data, we calculated the ratio of the central estimate (BMD or BMC) to the lower statistical confidence limit on the benchmark dose (BMDL) or concentration (BMCL) (Tables 1 and 3). This ratio (e.g., BMD/BMDL) provides a metric to compare the relative impact on estimated risk levels resulting from the selection of the BMD/BMC versus the BMDL/BMCL as the point of departure. Finally, among the studies that identified NOAELs, we compared the modeled BMDL and BMCL values with the empirical NOAELs as a means to investigate how using BMDL/BMCL values versus NOAELs compares with previous RfD/RfC methods based on the NOAEL approach.

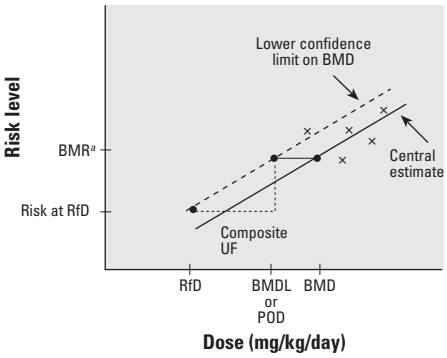


**Figure 1.** Linear extrapolation of risk from exposure at the RfD when the RfD is derived from benchmark modeling of quantal dose–response data. Assuming the relationship between risk of adverse outcome and dose is linear at low doses, we estimated risk from exposure at concentrations equal to established RfD and RfC values by extrapolating from the point represented by the BMR at the BMDL or BMCL to established RfD and RfC values. POD, point of departure.
[a]For quantal data, the BMR represents a percentage increase in risk compared with controls.

**Table 5.** Fitted BMD models and dose–response curve characterizations for 23 RfD/RfC assessments.

| Chemical | Reference value | End point | Fitted models[a] | Shape of dose–response curve |
|---|---|---|---|---|
| Antimony trioxide (U.S. EPA 1995b) | RfC | Quantal | Linear and Weibull[b] | Linear |
| EGBE (U.S. EPA 1999b, 1999c; NTP 1993, 1998) | RfC | Continuous | Power model ($k = 0.95$) | Linear |
| Methylene diphenyl diisocyanate (U.S. EPA 1998g, 1998h) | RfC | Quantal | Polynomial regression ($\beta_i = 0$)[c] | Linear |
| Methylmercury (U.S. EPA 2001a; NRC 2000) | RfD | Continuous | Power model ($k = 1$)[d] | Linear |
| Phenol (U.S. EPA 2002c, 2002d) | RfD | Continuous | Polynomial ($\beta_2 \cong 0$)[e] | Linear |
| Phosphoric acid (U.S. EPA 1995d) | RfC | Quantal | Linear and Weibull[b] | Linear |
| Tributyltin oxide (U.S. EPA 1997a, 1997b) | RfD | Continuous | Polynomial mean response ($\beta_i = 0$)[c] | Linear |
| Benzene (U.S. EPA 2003) | RfD | Continuous | Log-linear | Supralinear |
| Benzene | RfC | Continuous | Log-linear | Supralinear |
| Beryllium (U.S. EPA 1998a, 1998b) | RfD | Quantal | Exponential polynomial | Supralinear |
| 1,3-Butadiene (U.S. EPA 2002e) | RfC | Quantal | Weibull | Supralinear |
| Chloroform (U.S. EPA 2001b, 2001c) | RfD | Quantal | Quantal-linear | Supralinear |
| 1,1-Dichloroethylene (U.S. EPA 2002a, 2002b) | RfD | Quantal | Gamma | Supralinear |
| 1,1-Dichloroethylene | RfC | Quantal | Quantal-linear | Supralinear[f] |
| EGBE (U.S. EPA 1999b, 1999c; NTP 1993, 1998) | RfD | Continuous | Power model ($k = 0.66$) | Supralinear |
| Naphthalene (U.S. EPA 1998i, 1998j) | RfD | Continuous | Polynomial and power | Supralinear[g] |
| Chromium VI (particulates) (U.S. EPA 1998c, 1998d) | RfC | Continuous | Polynomial mean response | Sublinear |
| 1,3-Dichloropropene (U.S. EPA 2000c, 2000d) | RfD | Quantal | Gamma | Sublinear |
| 1,3-Dichloropropene | RfC | Quantal | Gamma | Sublinear |
| Hexachlorocyclopentadiene (U.S. EPA 2001d, 2001e) | RfD | Quantal | Log-logistic | Sublinear |
| Methyl methacrylate (U.S. EPA 1998e, 1998f) | RfC | Quantal | Polynomial mean response | Sublinear |
| Carbon disulfide (U.S. EPA 1995c) | RfC | Continuous | Weibull and polynomial | NA[h] |
| 1,1,1,2-Tetrafluoroethane (U.S. EPA 1995a) | RfC | Quantal | Weibull and polynomial (multistage) | NA[h] |

Abbreviations: EGBE, ethylene glycol monobutyl ether; NA, not available.
[a]Models were defined for an observed range of experimental data. [b]BMCs were obtained using both Weibull and linear models; the models gave similar goodness of fit to the data and BMC estimates. [c]Linear dose–response curve because assessment is based on a polynomial model with $\beta_i = 0$ for $i > 1$. [d]Model restricted to not allow supralinear forms. [e]Essentially linear dose–response curve because squared coefficient term of second-degree polynomial model is insignificantly small ($\beta_2 \cong 0$). [f]Shape of dose–response curve determined supralinear based on visual inspection; because slope parameter is small, curve approaches linear at low doses. [g]Shape of dose–response curve determined supralinear based on visual inspection; BMD model response function was not available. [h]Shape of dose–response curve information was not available; assumed linear or supralinear.

## Results

We found that 13 out of 23 (57%) of the BMD and BMC values were derived from quantal versus continuous data. A 10% additional risk or 10% change from control mean response was selected as the BMR for 17 of the 23 assessments, and a 5% BMR was selected for 3 of the remaining 6 assessments (Tables 6 and 7) [National Toxicology Program (NTP) 1993; U.S. EPA 1995a, 1995b, 1995c, 1995d, 1997a, 1998a, 1998c, 1998e, 1998g, 1998i, 1999b, 2000c, 2001a, 2001b, 2001d, 2002a, 2002e]. The BMR values for benzene's BMC and BMD and for phenol's BMD were based on a 1-standard-deviation change in acute lymphocyte count and maternal body weight, respectively, compared with the control mean (U.S. EPA 2002c, 2003).

Of the 21 BMD and BMC values for which sufficient dose–response information was available, we found that 16 (76%) were derived from dose–response data fitted to linear or supralinear models in the observed dose range (Table 5) (NRC 2000; NTP 1993, 1998; U.S. EPA 1995b, 1995d, 1997b, 1998b, 1998c, 1998d, 1998f, 1998h, 1998j, 1999c, 2000c, 2001c, 2001e, 2002b, 2002d, 2002e, 2003). Seven assessments were based on linear models (two linear models; three polynomial models with $\beta_i \cong 0$ for $i > 1$; two power models with $k \cong 1$), nine were based on supralinear models, and five were based on sublinear models. Sufficient information was not available to determine the shape of the fitted model for two assessments, carbon disulfide and 1,1,1,2-tetrafluoroethane (i.e., the response function and model parameters were not provided) (U.S. EPA 1995a, 1995c).

We calculated 17 RfD and RfC equivalent risk levels (for 14 compounds) assuming linear dose–response curves. These risk estimates ranged from 1 in 10,000 to 5 in 1,000 for the oral route of exposure for compounds with RfDs based on BMD values, and from 1 in 10,000 to 3 in 1,000 for inhalation for compounds with RfCs based on BMC values (Tables 6 and 7). Figures 2 and 3 present the RfD and RfC equivalent risk estimates on a

**Table 6.** Estimated risk levels from exposure at the RfD.

| Chemical | Point of departure (mg/kg/day) | BMR | UF | RfD (mg/kg/day) | Risk estimate | End point: quantal or continuous |
|---|---|---|---|---|---|---|
| Beryllium and compounds (U.S. EPA 1998a) | 0.46 | 10% | 300 | 0.002 | 1 in 10,000 | Quantal (small intestinal lesions) |
| Chloroform (U.S. EPA 2001b) | 1.2 | 10% | 100 | 0.01 | 1 in 1,000 | Quantal (fatty cyst formation in liver and elevated serum glutamate-pyruvate transaminase) |
| 1,1-Dichloroethylene (U.S. EPA 2002a) | 4.6 | 10% | 100 | 0.05 | 1 in 1,000 | Quantal [liver toxicity (fatty change)] |
| 1,3-Dichloropropene (U.S. EPA 2000c) | 3.4 | 10% | 100 | 0.03 | 1 in 100,000[a] | Quantal (chronic irritation of stomach) |
| Hexachlorocyclopentadiene (U.S. EPA 2001d) | 6.0 | 10% | 1,000 | 0.006 | 3 in $10^{9}$[a] | Quantal (chronic irritation of stomach) |
| Benzene[b] (U.S. EPA 2003) | 1.2 | 1 SD | 300 | 0.004 | 3 in 10,000 | Continuous (decreased lymphocyte count) |
| EGBE (U.S. EPA 1999b; NTP 1993) | 5.1 | 5% | 10 | 0.5 | 2 in 1,000 | Continuous (changes in mean corpuscular volume) |
| Methylmercury[c] (U.S. EPA 2001a) | 0.0009 | 5% | 10 | 0.0001 | 5 in 1,000 | Continuous (developmental neuropsychological impairment) |
| Naphthalene[d] (U.S. EPA 1998i) | 93 | 10% | 3,000 | 0.03 | — | Continuous (decreased mean terminal body weight) |
| Phenol (U.S. EPA 2002c) | 93 | 1 SD | 300 | 0.3 | 3 in 10,000 | Continuous (decreased maternal body weight gain) |
| Tributyltin oxide (U.S. EPA 1997a) | 0.03 | 10% | 100 | 0.0003 | 1 in 10,000 | Continuous (immunosuppression—decrease in IgE titer) |

EGBE, ethylene glycol monobutyl ether.
[a]Because IRIS assessment is based on sublinear dose–response curve, linearity was not assumed for low dose extrapolation, and risk estimate was derived from the BMD model response function. [b]BMR is expressed in terms of the standard deviation (in the absence of a clear definition for an adverse effect for this continuous end point, a default BMR of 1-standard-deviation change from the control mean was selected). This default definition of a BMR for continuous end points corresponds to an excess risk of approximately 10% for the proportion of individuals below the second percentile (or above the 98th percentile) of the control distribution for normally distributed effects. Benzene's oral $BMDL_{[ADJ]}$ was derived from the $BMCL_{[ADJ]}$ (8.2 mg/m$^3$) by route-to-route extrapolation with the assumptions that inhalation absorption was 50% and oral absorption was 100% in the dose range near the BMC. [c]BMR represents a 5% increased risk of neuropsychologic impairment compared to background. [d]Insufficient data available to estimate risk level (i.e., the response function, underlying distribution of the end point, or mean response and standard deviation of the treatment group and controls were not provided). Naphthalene's RfD in IRIS derived from the NOAEL (3,000-fold uncertainty factor) = 0.02 mg/kg/day; Tthe prospective RfD derived from the BMD (3,000-fold uncertainty factor) = 0.03 mg/kg/day.

**Table 7.** Estimated risk levels from exposure at the RfC.

| Chemical | Point of departure (mg/m$^3$) | BMR | UF | RfC (mg/m$^3$) | Risk estimate | End point: quantal or continuous |
|---|---|---|---|---|---|---|
| Antimony trioxide (U.S. EPA 1995b) | 0.074 | 10% | 300 | 0.0002 | 3 in 10,000 | Quantal (pulmonary toxicity, chronic interstitial inflammation) |
| 1,3-Butadiene (U.S. EPA 2002e) | 1.98 | 10% | 1,000 | 0.002 | 1 in 10,000 | Quantal (ovarian atrophy) |
| 1,1-Dichloroethylene (U.S. EPA 2002a) | 6.9 | 10% | 30 | 0.2 | 3 in 1,000 | Quantal [liver toxicity (fatty change)] |
| 1,3-Dichloropropene (U.S. EPA 2002c) | 0.72 | 10% | 30 | 0.02 | 3 in $10^{6}$[a] | Quantal (hyperplasia of nasal epithelium) |
| Methyl methacrylate (U.S. EPA 1998e) | 7.2 | 10% | 10 | 0.7 | 8 in 10,000[a] | Quantal (degeneration/atropy of olfactory epithelium) |
| Methylene diphenyl diisocyanate (U.S. EPA 1998g) | 0.06 | 10% | 100 | 0.0006 | 1 in 1,000 | Quantal (hyperplasia of the olfactory epithelium) |
| Phosphoric acid (U.S. EPA 1995d) | 3.4 | 10% | 300 | 0.01 | 3 in 10,000 | Quantal (bronchiolar fibrosis) |
| 1,1,1,2-Tetrafluoroethane (U.S. EPA 1995a) | 8,200 | 10% | 100 | 80 | 1 in 1,000 | Quantal (Leydig cell hyperplasia) |
| Benzene[b] (U.S. EPA 2003) | 8.2 | 1 SD | 300 | 0.03 | 3 in 10,000 | Continuous (decreased lymphocyte count) |
| Carbon disulfide[c] (U.S. EPA 1995c) | 19.7 | 10% | 30 | 0.7 | 3 in 1,000 | Continuous (peripheral nervous system dysfunction) |
| Chromium VI (particulates)[d] (U.S. EPA 1998c) | 0.034 | 10% | 300 | 0.0001 | — | Continuous (lactate dehydrogenase in bronchioalveolar lavage fluid) |
| EGBE (U.S. EPA 1999b; NTP 1993) | 380 | 5% | 30 | 13 | 2 in 1,000 | Continuous (changes in red blood cell count) |

EGBE, ethylene glycol monobutyl ether.
[a]Because IRIS assessment is based on sublinear dose–response curve, linearity was not assumed for low dose extrapolation, and risk estimate was derived from the BMC model response function. [b]BMC was based on a BMR of 1-standard-deviation change from the control mean (in the absence of a clear definition for an adverse effect for this continuous end point, a default BMR of 1-standard-deviation change from the control mean was selected). This default definition of a BMR for continuous end points corresponds to an excess risk of approximately 10% for the proportion of individuals below the second percentile (or above the 98th percentile) of the control distribution for normally distributed effects. [c]A 10% relative change was selected as an appropriate BMR for the nerve conduction velocity measurements because this level is about equal to a difference of 1 standard deviation from the control, and because a change of about 10% would likely raise concern in a clinical setting. [d]Insufficient data available to estimate risk level (i.e., the response function, underlying distribution of the end point, or mean response and standard deviation of the treatment group and controls were not provided).

logarithmic scale for these chemicals with linear or supralinear dose–response curves at the BMD/BMC. For four RfD and RfC equivalent risk levels (for 3 compounds), we used the sublinear dose–response model to calculate risk at the RfD or RfC. These risk estimates ranged from 3 in 1,000,000,000 to 1 in 100,000 from the oral route of exposure for compounds with RfDs based on BMD values, and from 3 in 1,000,000 to 8 in 10,000 from inhalation for compounds with RfCs based on BMC values (Tables 6 and 7).

Five of 21 reference values (24%) reviewed for this assessment corresponded to estimated risk levels greater than 1 in 1,000. Insufficient information was available to estimate risk from exposure at two reference values that were based on continuous response data, chromium VI particulates and naphthalene (i.e., the response function, underlying distribution of the end point, or mean response and standard deviation of the treatment group and controls were not provided). Figure 4 presents the distribution of estimated risk levels from human exposures at established RfD and RfC values for compounds with a linear or supralinear dose–response curve at the BMD. Risk estimates for four assessments derived from sublinear dose–response curves are presented in Tables 6 and 7.

Among the chemicals for which the RfD was based on a BMD, the BMD/BMDL ratio ranged from 1.3 to 3.0. Among the chemicals for which the RfC was based on a BMC, the BMC/BMCL ratio ranged from 1.1 to 2.3 (Tables 1 and 3). Thus, using the central estimate of the BMD or BMC (maximum likelihood estimate) instead of the lower statistical confidence limit (BMDL or BMCL) as the point of departure would result in a 1- to 3-fold difference in the estimated risk levels (Figures 2 and 3).

The effect level extrapolation factor (ELE) is an UF analogous to the LOAEL-to-NOAEL extrapolation factor. ELEs were applied in the assessments of three compounds, 1,3-butadiene (RfC), benzene (RfC and RfD), and ethylene glycol monobutyl ether (RfC) (Tables 2 and 4) (U.S. EPA 1999b, 2002e, 2003). Thus, no ELE factor was assigned for 16 of 17 assessments that were based on a BMR of 10%.

When we compared the points of departure (i.e., BMDL/BMCL values) with the NOAELs, we found that the points of departure were higher than the NOAELs in 10 of the 14 studies with identified NOAELs (Figure 5). The BMDL values were up to 4.6 times higher than the empirical NOAELs (range, 0.5–4.6), and the BMCL values were up to 3.9 times higher than the empirical NOAELs (range, 0.2–3.9) (Tables 1 and 3).

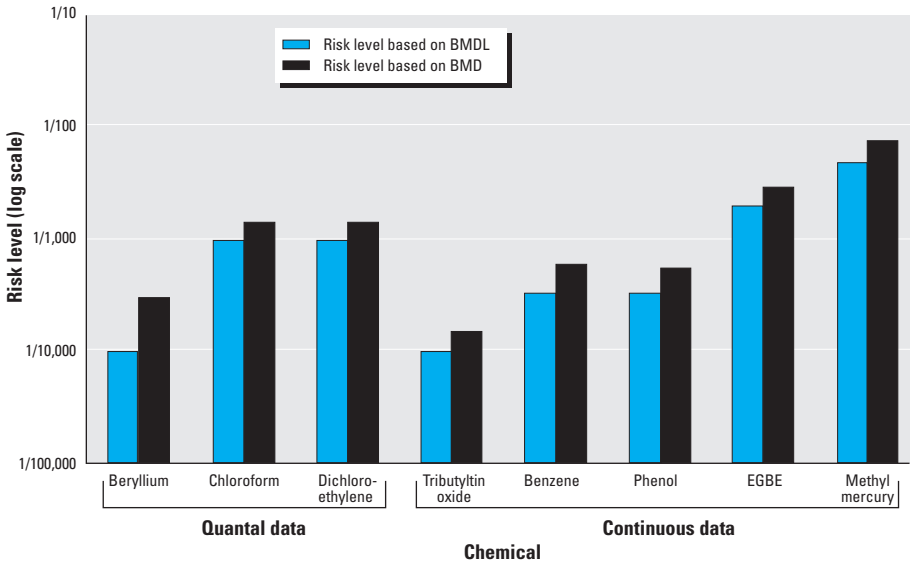


**Figure 2.** Estimated risk levels from exposure at the RfD based on the BMD and the BMDL derived from linear or supralinear dose–response curves. EGBE, ethylene glycol monobutyl ether.

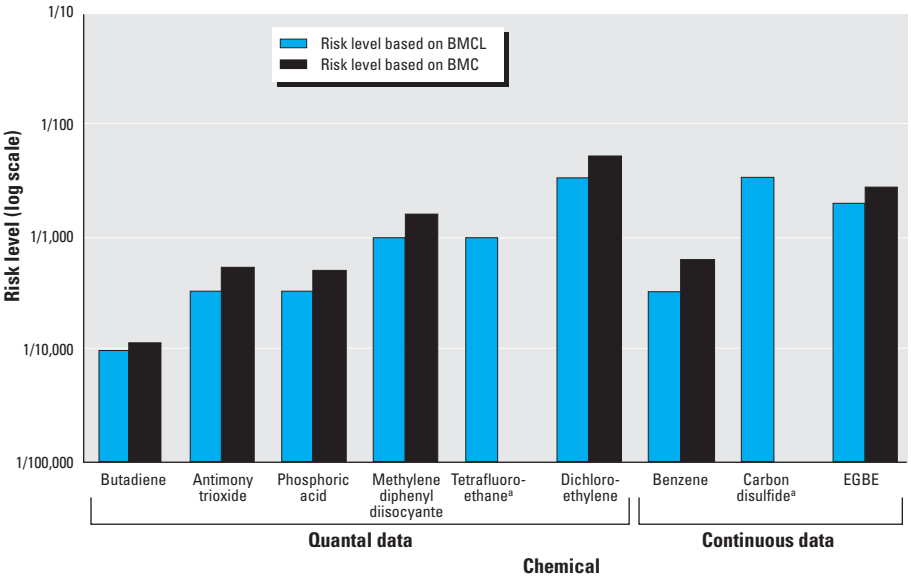


**Figure 3.** Estimated risk levels from exposure at the RfC based on the BMC and the BMCL derived from linear or supralinear dose–response curves. EGBE, ethylene glycol monobutyl ether.
[a]BMC central estimate not provided by the U.S. EPA.

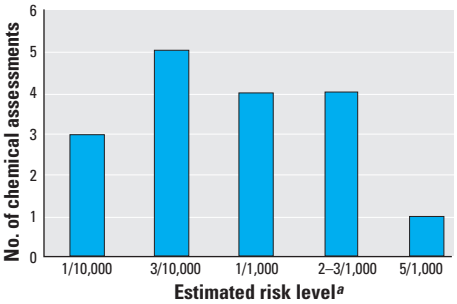


**Figure 4.** Distribution of estimated risk levels from human exposures at established RfD and RfC values for reference doses derived from linear or supralinear dose–response curves.
[a]Risk estimates for assessments based on sublinear dose–response curves are not included.

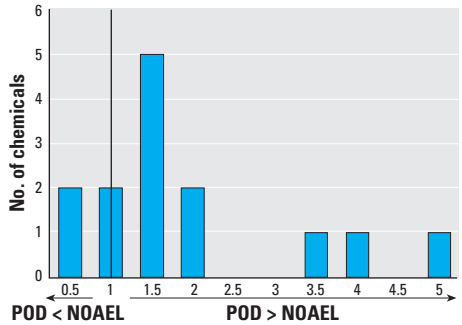


**Figure 5.** Ratio of the points of departure (PODs) to empirically derived NOAELs. PODs based on benchmark modeling.

## Discussion

To determine whether U.S. EPA reference values represent negligibly small risk levels, we reviewed and synthesized currently available risk assessment information on chemicals for which established RfD and RfC values are based on BMD modeling. For RfDs and RfCs derived from linear or supralinear dose–response curves, our risk estimates ranged from 1 in 10,000 to 5 in 1,000 for the oral route of exposure, and from 1 in 10,000 to 3 in 1,000 for inhalation. Risk estimates for RfDs and RfCs derived from sublinear dose–response curves ranged from 3 in 1,000,000,000 to 8 in 10,000. Twenty-four percent of reference values reviewed for this assessment corresponded to estimated risk levels greater than 1 in 1,000. The estimated risk of exposure to 1,1-dichloroethylene at its RfC, for example, corresponded to a 3-in-1,000 risk of adverse effect [liver toxicity (fatty change)].

The BMD methodology is the first step in the development of continuous risk functions that can be used to estimate risks at different exposures rather than using an RfD/RfC approach, which has limited use in the decision-making process. For example, BMD and BMC values that are based on the same level of adverse response (e.g., BMR = 10%) can be used to rank the potential hazard of exposure to multiple toxicants. Further application of BMD models, such as has been done here, can be used for estimating adverse noncancer health outcomes from different exposures for other risk-ranking exercises, regulatory policy development, and cost/benefit analyses.

The U.S. EPA used a variety of fitted models to calculate the BMD/BMC values found in IRIS (e.g., *K* power, linear, quantal-linear, exponential polynomial, and Weibull). To compare RfD and RfC equivalent risk levels, we assumed that the dose–response curves for the chemicals in our assessment group are linear at doses below the point of departure. This assumption could have resulted in both underestimates and overestimates of risk. In the case of a supralinear dose–response curve at low doses, for example, this assumption may have resulted in an underestimate of risk. Among the chemicals we reviewed, 9 of the 21 assessments with sufficient information to determine the shape of the dose–response curve were based on supralinear functions. In the case of a sublinear dose–response, this assumption may have resulted in a marked overestimate of risk. For the 5 assessments based on sublinear dose–response curves, therefore, we did not assume linearity for low dose extrapolation and risk estimation.

We believe that the assumption of linearity in the relevant part of the dose–response curve is justified and useful to compare risk levels among this group of compounds. Seventy-six percent of BMD and BMC values considered in this assessment were derived from dose–response data fitted to linear or supralinear models. Furthermore, the range of extrapolation for the RfD/RfC calculations was not large among this group, with most based on points of departure extrapolated to 2 orders of magnitude or less (7 were extrapolated to 1 order of magnitude, 13 were extrapolated to 2 orders of magnitude, and 3 were extrapolated to 3 orders of magnitude). The average and median composite UFs among the compounds in our assessment are 340 and 100, respectively. This implies that even if the dose–response curve for a particular compound is not strictly linear at much lower doses, we could expect the potential impact on the risk estimate to be relatively small.

Current U.S. EPA methodology for reference value derivation assumes that the established RfDs/RfCs represent negligibly small risk levels. For assessments that have linear dose–response curves, the extrapolation from the point of departure is typically 2 orders of magnitude or less. Therefore, for the RfD/RfC values to represent risk levels that are below regulatory concern, the dose–response curve would have to drop off sharply after the point of departure. This assumption seems unlikely, especially given our finding that a large number of the assessments we reviewed (9 of 21) were based on supralinear dose–response functions. Although this supralinearity may carry significant implications for risk assessment, more research is needed to determine whether these dose–response relationships remain supralinear at very low doses. On the other hand, assessments based on dose–response curves that are not monotonic may have sublinear or stepwise relationships below the observed data.

Using the BMDL or BMCL as the point of departure in the risk assessment of noncarcinogenic compounds rather than the BMD or BMC central estimate is generally characterized as a conservative assumption (in the health-protective sense). We found that using the central estimate of the BMD (maximum likelihood estimate) instead of the lower bound estimate as the point of departure results in a 1- to 3-fold difference in the risk estimates. According to the U.S. EPA draft BMD guidelines (U.S. EPA 2000a), a lower confidence limit is placed on the BMD to obtain a dose (BMDL) that assures with high confidence (e.g., 95%) that the BMR is not exceeded. This process of using the BMDL rewards better experimental design and procedures that provide more precise estimates of the BMD, resulting in tighter confidence intervals and thus BMDLs that are closer to the central estimate. Our results suggest that the current practice of using the statistical lower bound estimate versus the maximum likelihood estimate as the point of departure is reasonable and does not substantially bias the risk estimate.

For carcinogens, the U.S. EPA typically develops a linear estimate of the slope of the dose–response curve, under the assumption that the curve is linear at low doses. This allows for quantification of risk at any given level of exposure. The U.S. EPA has defined 1 in 1,000,000 excess cancer risk as a *de minimis* risk level for cancer (Caldwell et al. 1998; Clean Air Act Amendments 1990; Fiori and Meyerhoff 2002; U.S. EPA 1991), although regulatory actions are sometimes limited to instances where risk exceeds 1 in 100,000. Among compounds in IRIS with RfDs and RfCs based on BMD modeling, however, we found risk estimates as great as 5 in 1,000. Although noncancer outcomes may in some instances be reversible and considered less severe, this finding calls into question the assumption that noncancer RfD and RfC values represent "acceptable levels" of exposure. In addition, some of the noncancer health end points considered in this assessment are severe and irreversible events, for example, ovarian atrophy (1,3-butadiene) and developmental neuropsychologic impairment (methylmercury), highlighting the need for a renewed discussion within the public health community about what should be considered an "acceptable level" of risk from exposure to toxicants with noncancer health end points.

Most of the BMDLs and BMCLs used as points of departure in IRIS are based on 10% BMRs, many with values higher than the empirically derived NOAELs. This research should help inform discussions about whether this level of BMR is adequately protective of the public health, and whether human exposures at concentrations equal to the resulting reference values do in fact represent negligibly small risk levels.

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